Amendments to the specification:

Rewrite paragraphs at page 5, line 17 – page 8, line 20, as:

Figure 1 depicts a comparative study of lymphokine activated killer cell (LAK cell) mediated cytotoxicity on glioma cells. One part of the cells was incubated with the TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30, the other part was additionally treated with CCNU. The figure clearly points out that the cytotoxic activity of LAK cells treated with CCNU in combination with TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 is superior compared to LAK cells treated with only TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30.

$5x10^6$ PBMC (peripheral blood mononuclear cells) were cultivated in 4 µL RPMI 1640 medium supplemented with 10% foetal calf serum, in the presence of 10 ng/ml rh IL-2 (recombinant human interleukin 2), in 5% CO_2 atmosphere at 37°C. The first 3 days 5 µM TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 was added. After that one part of the cells was incubated with 10 µM CCNU for an additional 6 h. Cell-mediated cytotoxicity, quantified by CARE-LASS assay (Lichtenfels et al. 1994), of LAK cells treated with TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 (horizontal hachures) was compared to LAK cells treated with TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 in combination with CCNU (diagonal hachures). Indicated are means ± SD of quadruplicates.

Figure 2 depicts a comparative study of lymphokine activated killer cell (LAK cell) mediated cytotoxicity on glioma cells. One part of the cells was incubated with the TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 the other part was subsequently treated with Temozolomid (TMZ). The figure clearly points out that the cytotoxic activity of LAK cells treatment with temozolomid after the treatment with TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 is superior compared to LAK cells treated only with TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30.

$5x10^6$ LAK were cultivated in RPMI medium supplemented with 10% foetal calf serum, in the presence of 10 ng/ml rh IL-2 (recombinant human interleukin 2), in 5% CO_2 atmosphere at 37°C. The first 3 days 5 µM TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 was added. Cell-mediated cytotoxicity was then quantified by CARE-LASS assay (Lichtenfels et al. 1994) in one part of the cells without further treatment (only TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30, horizontal hachures), in the other part in the presence of 30 µM temozolomid (TMZ, diagonal hachures). Indicated are means ± SD of quadruplicates.

Figure 3 depicts survival data of patients treated with the TGF-beta antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 after treatment with temozolomide according to standard schedule compared to the median overall survival time of patients treated with temozolomide only according to standard schedule. Survival time is given from start of first chemotherapy after tumor recurrence. Median overall survival time in the clinical study is evaluated from 3 patients with anaplastic astrocytoma and 10 patients with glioblastoma. The survival data are compared to the survival data of the literature. Our data reveal longer median overall survival times if applying TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 following temozolomide than the comparable published data for temozolomide alone: 146.6 weeks vs. 42.0 weeks for patients suffering from anaplastic astrocytoma and 45.1 weeks versus 32.0 weeks for patients suffering from glioblastoma.

Figure 5 depicts the specific lysis of tumor cells in an in vitro assay with A-172 cell line performed according to descriptions in example 7 in a ratio of effector cells to target cells of 1.25 :1. Antisense oligonucleotide with Sequence Id. No. 30 was under test at a concentration of 5 microMol enhancing cell lysis. In contrast CCNU at a concentration of 10 µM inhibited LAK cell induced cell lysis, which indicates its immunosuppressive effect. Surprisingly, the cytolytic effect of ~~Seq. Id. No.~~ SEQ ID NO: 30 (5 microM) was enlarged supraadditively in combination with CCNU (10 µM) (specific cell lysis of control:2.6 %, CCNU 0.5 %, ~~Seq. Id. No.~~ SEQ ID NO: 30: 4.4 %, ~~Seq. Id. No.~~ SEQ ID NO: 30 in combination with CCNU: 13.3 %).

Figure 6 depicts the specific lysis of tumor cells in an in vitro assay with Hup-T3 cell line

performed according to descriptions in example 7 in a ratio of effector cells to target cells of 10:1. Antisense oligonucleotide with Sequence Id. No. 30 was under test at a concentration of 5 microM enhancing cell lysis. In contrast gemzar at a concentration of 20 µg/ml inhibited LAK cell induced cell lysis, which indicates its immunosuppressive effect. Surprisingly, the cytolytic effect of ~~Seq. Id. No.~~ SEQ ID NO: 30 (5 microM) was enlarged supraadditively in combination with gemzar (20 µg/ml) (specific cell lysis of control: 32.9 %, gemzar 34.5 %, ~~Seq. Id. No.~~ SEQ ID NO: 30: 59.5 %, ~~Seq. Id. No.~~ SEQ ID NO: 30 in combination with gemzar: 75.4 %).

Figure 7 depicts the specific lysis of tumor cells in an in vitro assay with A-172 cell line performed according to descriptions in example 7 in a ratio of effector cells to target cells of 10 :1. Antisense oligonucleotide with Sequence Id. No. 30 was under test at a concentration of 5 microMol enhancing cell lysis. A very small increase of LAK cell induced cell lysis could be observed with temozolomide at a concentration of 50 µM. But, surprisingly, the cytolytic effect of ~~Seq. Id. No.~~ SEQ ID NO: 30 (5 microM) was enlarged supraadditively in combination with temozolomide (50 µM) (specific cell lysis of control: 25.2 %, temozolomide 31.3 %, ~~Seq. Id. No.~~ SEQ ID NO: 30: 39.2 %, ~~Seq. Id. No.~~ SEQ ID NO: 30 in combination with temozolomide: 50.4 %).

Figure 8 depicts the specific lysis of tumor cells in an in vitro assay with A-172 cell line performed according to descriptions in example 7 in a ratio of effector cells to target cells of 2.5 :1. Antisense oligonucleotide with Sequence Id. No. 30 was under test at a concentration of 5 microMol enhancing cell lysis. A very small increase of LAK cell induced cell lysis could be observed with vincristine at a concentration of 0.04 pmol/ml. But, surprisingly, the cytolytic effect of ~~Seq. Id. No.~~ SEQ ID NO: 30 (5 microM) was enlarged supraadditively in combination with vincristine (0.04 pmol/ml) (specific cell lysis of control: 10.1 %, vincristine 12.6 %, ~~Seq. Id. No.~~ SEQ ID NO: 30: 13.9 %, ~~Seq. Id. No.~~ SEQ ID NO: 30 in combination with vincristine: 20.5 %).

Figure 9 depicts the specific lysis of tumor cells in an in vitro assay with NCL-H661 cell line performed according to descriptions in example 7 in a ratio of effector cells to target cells of 1.25 :1. Antisense oligonucleotide with Sequence Id. No. 14 was under test at a concentration of 5

microMol enhancing cell lysis. In contrast taxotere reduced LAK induced cell lysis at a concentration of 0.37 µg/ml. But in this case the cytolytic effect of ~~Seq. Id. No.~~ SEQ ID NO: 14 (5 microM) was reduced in combination with taxotere (0.37 µg/ml) (specific cell lysis of control: 49.6 %, taxotere 30.5 %, ~~Seq. Id. No.~~ SEQ ID NO: 14: 65.3 %, ~~Seq. Id. No.~~ SEQ ID NO: 30 in combination with taxotere: 39.7 %).

Figure 10 depicts the specific lysis of tumor cells in an in vitro assay with A-172 cell line performed according to descriptions in example 7 in a ratio of effector cells to target cells of 5 :1. Antisense oligonucleotide with Sequence Id. No. 30 was under test at a concentration of 5 microMol enhancing cell lysis. In contrast procarbacine reduced LAK induced cell lysis at a concentration of 3 nmol/ml. But in this case the cytolytic effect of ~~Seq. Id. No.~~ SEQ ID NO: 30 (5 microM) was reduced in combination with procarbacine (3 nmol/ml). (specific cell lysis of control: 8.31 %, procarbacine 6.1 %, ~~Seq. Id. No.~~ SEQ ID NO: 14: 16.4 %, ~~Seq. Id. No.~~ SEQ ID NO: 30 in combination with procarbacine: 5.7 %).

Rewrite paragraphs at page 36, line 11 – page 37, line 18, as:

In one ebodiment a pharmaceutical composition for the treatment of glioma, glioblastoma and/or anaplastic astrocytoma comprises a combination of at least one immunostimulator, more preferred an antagonist of TGF-beta, even more preferred an antisense oligonucleotid of TGF-beta and most preferred, an antisense oligonucleotide identified in the sequence listing under ~~Seq. Id. No.~~ SEQ ID NO: 1-127 and even more preferred the sequences with ~~Seq. Id. No.~~ SEQ ID NO: 22-48 and at least one substance inhibiting cell proliferation and/or inducing cell death preferably selected from the group of temozolomide, ACNU, BCNU, CCNU, vinblastine, vincristine, vindesine and their active derivatives, 5-fluorouracile, 5-fluorodeoxiuridine, cytarabine, gemicitabine liposomal pegylated doxorubicine, procarbazine and vincristin.

In another embodiment the antineoplastic chemotherapeutic agents procarbazine, CCNU and vincristin are together with the immunostimulator, more preferred an antagonist, even more preferred an antisense oligonucleotid of TGF-beta and most preferred, an antisense

oligonucleotide identified in the sequence listing under ~~Seq. Id. No.~~ SEQ ID NO: 1-127 and even more preferred the sequence with ~~Seq. Id. No.~~ SEQ ID NO: 22-48 are the components of a pharmaceutical composition. The dosage in this embodiment is about 40 mg/m^2 to about 80 mg/m^2 of procarbazine p.o. (days about 8 to about 21), about 80 to about 120 mg/m^2 CCNU, p.o. (about day 1), vincristin from about 1.2 mg/m^2 to about 1.8 mg/m^2 p.o. (day 1) with a maximum of about 2 mg/m^2 i.v. on about day 8, and about day 29. The immunostimulator is given before, with or after the administration of these three substances.

In another embodiment this cycle is repeated after about 6 to about 8 weeks once or several times.

In a further preferred embodiment the at least one immunostimulator more preferred an antagonist, even more preferred an antisense oligonucleotid of TGF-beta and most preferred, an antisense oligonucleotide identified in the sequence listing under ~~Seq. Id. No.~~ SEQ ID NO: 1-127 and even more preferred the sequences with ~~Seq. Id. No.~~ SEQ ID NO: 22-48 and telozolomide are the parts of a pharmaceutical composition. In this case the dosage of temozolomide for the treatment of unwanted neoplasms more preferred glioma, glioblastoma and/or anaplaystic astrocytoma is from about 120 to about 180 mg/m^2, p.o. on day 1 to 5 of a cycle. In a more preferred embodiment the immunostimulator is administered from about 1 µg/kg/day to about 50 mg/kg/day. The cycle is repeated after about 3 to 5 weeks.

In a more preferred embodiment of the above mentioned embodiments for the treatment of neoplöasms such as glioma, glioblastoma and/or anaplastic astrocytoma the immunostimulator is an antagonist of TGF-beta yet more preferred an antisense oligonucleotide identified in the sequence listing under ~~Seq. Id. No.~~ SEQ ID NO: 1-127 and most preferred the oligonucleotides identified with the ~~Seq. Id. No.~~ SEQ ID NO: 22 to 48.

Rewrite page 38, paragraph 4, as:

In a more preferred embodiment of the above mentioned embodiments for the treatment of pancreatic

neoplasm the antagonist is an antagonist of TGF-beta yet more preferred an antisense oligonucleotide identified in the sequence listing under ~~Seq. Id. No.~~ SEQ ID NO: 1-127 and even more preferred the sequence with ~~Seq. Id. No.~~ SEQ ID NO: 22-48.

Rewrite page 39, paragraph 4, as:

In a more preferred embodiment of the above mentioned embodiments for the treatment of NSCLC the immunostimulator is an antagonist of TGF-beta yet more preferred an antisense oligonucleotide identified in the sequence listing under ~~Seq. Id. No.~~ SEQ ID NO: 1-127 and even more preferred the sequences with ~~Seq. Id. No.~~ SEQ ID NO: 1 to 21 are administered according to schedules as described above.

Rewrite the paragraphs at page 40, line 27 – 41, line 9, as:

In even more preferred embodiments of the above mentioned embodiments for the treatment of melanoma the immunostimulator is an antagonist of TGF-beta yet more preferred an TGF-beta antisense oligonucleotide identified in the sequence listing under ~~Seq. Id. No.~~ SEQ ID NO: 1-127 and even more preferred the sequence with ~~Seq. Id. No.~~ SEQ ID NO: 1 to 78.

Further preferred embodiments are pharmaceutical compositions according to this invention for the treatment of neoplasms such as prostate cancer. In a preferred embodiment the at least one substance inhibiting cell proliferation and/or inducing cell death is selected from the group of docetaxel, estramustinephosphate and mitoxantrone.

In even more preferred embodiments of the above mentioned embodiments for the treatment of neoplasms such as prostate cancer the antagonist is an antagonist of TGF-beta yet more preferred an antisense oligonucleotide identified in the sequence listing under ~~Seq. Id. No.~~ SEQ ID NO: 1-127 and even more preferred the sequences with ~~Seq. Id. No.~~ SEQ ID NO: 1-21.

Rewrite the paragraphs at page 49, line 11 – 51, line2, as:

Surgical planning was based on computer tomography or magnetic resonance images. The

perforated part of the catheter was placed in the solid, enhancing area of the tumor. Ventricles, cysts, resection cavities from prior surgical interventions, blood vessels and eloquent brain areas had to be avoided by the catheter trajectory. The catheter was introduced through a standard burr hole into the center of the largest tumor lesion. The distal end of the catheter was passed several centimetres under the galea through the skin and filled with saline. TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 was administered intratumorally as a continuous high-flow microperfusion using an external pump system, Graseby 3200 (Smith Medical, London, GBM). The application system was removed after the end of the infusion. For safety assessment patients were followed up for 28 days. Post-study MRI and survival data until death were collected by the investigators.

1. Example

47 years old male who was diagnosed with a histologically grade III anaplastic astrocytoma received a combination therapy of several antineoplastic agents and TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30. The antineoplastic agents administered were ACNU together with tenoposide, temozolomide, and PEG-ylated liposomal doxorubicin (Caelyx®). ACNU was administered partly parallel with tenoposide with 90 mg/m^2 ACNU on the first day of each cycle and 60 mg/m^2 of tenoposide on days 1-3 of each cycle. Each cycle comprised 42 days, 4 of these cycles were realized. About 2 years later the patient was treated with 3 cycles of temozolomide. Each cycle of 28 days started with the administration of temozolomide 75 mg/m^2 from day 1-5. About 8 months after this treatment PEG-ylated liposomal doxorubicin (Caelyx®) was administered in 5 cycles of 42 days, with 20 mg/m^2 on day 4 and day 14 of the cycle, followed by a week with 160 mg tamoxifen administration in the morning and in the evening.

The therapy with these antineoplastic agents according to standard schedules was finally without success and therefore the patient was included into the study with TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 showing surprising success. At the startpoint

of this study the magnetic resonance imaging showed three tumors in the left frontal lobe and an additional tumor in the right hemisphere and an overall oedema. After the chemotherapy with the above mentioned antineoplastic agents one cycle of TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 (10 µM in steril pyrogen free isotonic 0.9% NaCl solution, 4 µL/min, total of 1.42 mg in 4 days) was applied intratumorally by an implanted catheter into the largest nodule. Six months after start of TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 a clear reduction of the largest tumor lesion could be diagnosed. Although not individually targeted by the catheter, the three smaller tumors also disappeared completely. Additionally, the oedema had decreased. 17 months after the first application of TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 the largest tumor was hardly measurable anymore. Four months later a complete response was assessed by 3 independent specialists. These findings were accompanied by clinical improvement. The patient died due to a myocardial infarction without signs of tumor recurrence and had experienced an overall survival of 195 weeks after first recurrence and 208 weeks after diagnosis of anaplastic astrocytoma.

2. Example

Male patient 45 years old was diagnosed with anaplastic astrocytoma (WHO grade III). The diagnosis was followed by surgery and radiotherapy. 3 times 200 mg/m^2 Temozolomide was administered according to a standard schedule during two months. Again this therapy was without success. Therefore the patient was included into the study with TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30. Two cycles of this oligonucleotide with a concentration of 80 µM and a flow of 8 µl/min was administered for each 4 days through a catheter placed inside the tumor tissue. Afterwards the patient received ten additional cycles within four months. Following the last cycle of the oligonucleotide, approximately 10 months after the first oligonucleotide treatment, the patient received seven cycles of liposomal doxorubicin (Caelyx®).

Rewrite page 51, lines 14-23, as:

Comparison of survival data of patients treated with antineoplastic agents in combination with antagonists of factors negatively influencing the immune system (here: an antisense oligonucleotide of TGF-beta with the sequence Id. No. 30) to literature data for treatment with antineoplastic alone. Survival time is given from start of first chemotherapy after tumor recurrence. Median overall survival time of all patients treated with antineoplastic agents and TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 (anaplastic astrocytom: 8 patients, glioblastoma, 23 patients) are compared to the most current literature data (Theodosopoulos, P.V. et al. 2001).

Rewrite the paragraphs at page 52, line 11 – 53, line20, as:

Summary of patients' characteristics from the study. Patients 01, 13 and 16 received each two cycles of pegylated liposomal doxorubicin (Caelyx®), patient 14 two cycles of PCV (procarbazine, lomustine (CCNU), vincristine) after TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 treatment, all other patients had no anti-tumor therapy after oligonucleotide treatment. Patient 17 received 10 additional oligonucleotide cycles. After the last cycle of the oligonucleotide the patient received 7 cycles of pegylated liposomal doxorubicin.

Reduction of tumor volumes of patients 04 and 17 was more than 80%. Tumor volume was assessed by measurement of the largest cross-sectional diameter of the enhancing lesion in the first layer and the largest cross-sectional diameter perpendicular to the first in the same plane and layer. For the third dimension, the largest cross-sectional diameter of all further planes perpendicular to the first one was determined.

Compared to literature data for the treatment with antineoplastic agents alone the survival data show clearly enhanced survival of patients treated with one or more antineoplastic agents (e.g. temozolomide and/or procarbazine) before the administration of TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30.

The data are calculated after start of chemotherapy. According to this approach the median overall survival in our study was 147 weeks for AA and 42.4 weeks for GBM. The data reveal longer median overall survival times if applying the oligonucleotide following chemotherapy (mainly temozolomide) than the comparable published data for temozolomide alone, for which the most recent and accurate survival data are available: about 147 weeks versus 42 (Theodosopoulos, P.V. et al. 2001) weeks for anaplastic astrocytoma, and 45 weeks versus about 32 weeks (Theodosopoulos, P.V. et al. 2001; Yung, W.K. et al. 2000; Yung, W.K. 2000; Brandes, A.A. et al. 2001) for GBM, respectively.

These results surprisingly show that there is a clear survival advantage of patients treated with a combination of the antagonist, TGF-beta 2 specific antisense oligonucleotide with ~~Seq. Id. No.~~ SEQ ID NO: 30 and at least one further antineoplastic agent (e.g. temozolomide) in patients suffering from neoplasm, e.g. AA (mean overall survival of 146.6 weeks versus 90 weeks for all anaplastic astrocytoma patients).

Rewrite page 61, lines 4-14, as:

Cell-mediated cytotoxicity was quantified by the CARE-LASS assay (Lichtenfels et al. 1994) using the NSCLC (non small cell lung carcinoma cell) line NCI-H661, the glioma cell line A-172, and the pancreatic cancer cell line Hup-T3 as target cells. NCI-H661 cells were pretreated with 5 µM TGF (transforming growth factor)-beta 1 specific antisense phosphorothioate oligodeoxynucleotide (PTO) ~~Seq. Id. No.~~ SEQ ID NO: 14. A-172 and Hup-T3 cells were pretreated with 5 µM TGF-beta 2 specific antisense phosphorothioate oligodeoxynucleotide ~~Seq. Id. No.~~ SEQ ID NO: 30 in medium at 5% CO2 and 37°C for 3 days according to the cell line suppliers' instructions. Additionally, for Hup-T3 cells 3 µg/ml Lipofectin® were used to enhance cellular uptake of the PTO. Untreated cells and cells treated with 3 µg/ml Lipofectin® were used as controls.